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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,608	12/14/2006	Antonio Martinez Martinez	ABG 3008	1313

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EXAMINER	
LEE, JAE W	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
04/15/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/550,608	MARTINEZ ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-12 and 30-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-12 and 30-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

In response to the previous Office action, a non-Final rejection (mailed on 10/14/2009), Applicants filed a response and amendment received on 01/07/2010. Said amendment canceled Claims 2, 3, 5 and 13-29, amended Claims 1, 4 and 6-12, and added Claims 30-38. Thus, Claims 1, 4, 6-12 and 30-38 are at issue and present for examination.

Applicants' arguments filed on 01/07/2010, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Drawings

The previous objection to the drawings for failing to show details of Figure 1 is withdrawn because Applicants provided a replacement sheet for Figure 1 with corrected contrast.

Claim Objections

The previous objection of Claims 1, 4 and 6-12 for the recitation of "FGFR3" is withdrawn by virtue of Applicants' amendment.

The previous objection of Claim 1 (4 and 6-12 dependent therefrom) for the recitation of the phrase, "and normal references values in samples from subjects without bladder transitional cell carcinoma", is withdrawn by virtue of Applicants' amendment.

The previous objection of Claims 4 and 6-12 for the recitation of "Method according to…" is withdrawn by virtue of Applicants' amendment.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of Claim 4 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn by virtue of Applicants' amendment.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The previous rejection of Claims 1, 4 and 6-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn by virtue

of Applicants' amendment which deleted the phrase "to determine the stage or severity of this cancer in an individual".

Claims 30-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for an *in vitro* method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual or to monitor the effect of the therapy administered to the individual with this cancer, that comprises: a) the detection and/or quantification of the FGFR3 protein in a sample of an individual, wherein the sample is a bladder tissue or urine, and b) the comparison of the amount of FGFR3 protein, of detected in a sample of an individual, with normal reference values in samples from subjects without bladder transitional cell carcinoma; wherein, increased levels of FGFR3-protein relative to normal reference values are indicative of bladder TCC, does not reasonably provide enablement for an in vitro method *to assess the stage or severity of this cancer in an individual*, that comprises: a) the detection and/or quantification of the FGFR3 protein in a sample of an individual, wherein the sample is a bladder tissue or urine, and b) the comparison of the amount of FGFR3 protein, of detected in a sample of an individual, with their normal reference values; wherein, increased levels of FGFR3-protein relative to normal reference values are indicative of bladder TCC, and normal reference values in samples are from subjects without bladder transitional cell carcinoma (italicized for added emphasis). The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The breath of the claims. Claims 30-38 are so broad as to encompass an in vitro method *to assess the stage or severity of this cancer in an individual*, that comprises: a) the detection and/or quantification of the FGFR3 protein in a sample of an

individual, wherein the sample is a bladder tissue or urine, and b) the comparison of the amount of FGFR3 protein, of detected in a sample of an individual, with their normal reference values; wherein, increased levels of FGFR3-protein relative to normal reference values are indicative of bladder TCC, and normal reference values in samples are from subjects without bladder transitional cell carcinoma (italicized for added emphasis). The enablement provided is not commensurate in scope with the claim because the specification lacks any disclosure with regard to how specific quantities of FGFR3 correlate to different grades/stages of tumor. In the instant case, the specification enables for an in vitro method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual, or to monitor the effect of the therapy administered to the individual with this cancer.

The amount of direction or guidance presented and the existence of working examples. The specification discloses an in vitro method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual, or to monitor the effect of the therapy administered to the individual with this cancer. However, the specification fails to provide any correlation regarding specific quantities of FGFR3 that can be used to assess the stage, i.e. grade, or severity of bladder TCC in an individual. Without such correlation, one of skill in the art would not know how to "use" the instant methods as claimed because it is unclear how much of the FGFR3 protein have to be differentially expressed to be classified as stage/grade 1 or 2. It is noted by the Examiner that the disclosure of the instant specification is limited to an in vitro method of "detecting" the FGFR3 protein.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. While the art discloses several methods of detecting and quantifying FGFR3 proteins, neither the specification nor the art provide a correlation between specific quantities of FGFR3 and different stages, i.e. grade, or severity of bladder TCC in an individual. In support of this notion, the Examiner presents a post-filing evidentiary reference of Matsumoto et al. (Fibroblast growth factor receptor 3 protein expression in urothelial carcinoma of the urinary bladder, exhibiting no association with low-grade and/or non-invasive lesions, Oncol Rep. 2004 Nov;12(5):967-71, Retrieved from the Internet <URL:http://www.ncbi.nlm.nih.gov/pubmed/15492779?ordinalpos=85&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum> on 10/05/2009), which states that "no statistically significant relationship was found between FGFR3 expression and tumor grade, invasion" (see Abstract, lines 12-13) (this reference has been previously included in the office action mailed on 10/14/2009). Without such correlation, one of skill in the art would not know how to "use" the instant methods as claimed because it is unclear how much of the FGFR3 protein have to be differentially expressed to be classified as stage/grade 1 or 2.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of detecting and quantifying FGFR3 proteins were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process to determine specific ranges of the FGFR3 protein that is differentially expressed in thousands of bladder TCC patients

to build a correlation between specific quantities of FGFR3 and different stages, i.e. grade, or severity of bladder TCC in an individual. In the absence of such correlations, one of skill in the art would have to test an essentially infinite number of patients with different stages of bladder TCC progression, and to assess which specific ranges of FGFR3 protein expression correlate with each stage of the bladder TCC.

Therefore, taking into consideration the broad scope of the claim, the lack of guidance, the amount of information provided, the lack of knowledge about said correlation between specific quantities of FGFR3 and different stages, i.e. grade, or severity of bladder TCC in an individual, and the high degree of unpredictability associated with making such correlation, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The previous rejection of Claims 1, 4 and 6-12 under 35 U.S.C. 103(a) as being unpatentable over Sturla et al. (FGFR3IIIS: a novel soluble FGFR3 spliced variant that modulates growth is frequently expressed in tumour cells, British Journal of Cancer (2003) 89, pages 1276 – 1284, published online on 09/30/2003) in view of KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007), is withdrawn because Applicants' definition of what constitutes an FGFR3 protein encompasses FGFR3IIIb and FGFR3IIIc. As such, the Examiner is withdrawing the instant rejection of record as FGFR3IIIS is not within the scope of this definition.

Claims 1, 4 and 6-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cappellan et al. (Frequent Activating Mutations of FGFR3 in Human B adder and Cervix Carcinomas, Nature Genetics, Vol. 23, September 1999, see IDS) in view of KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007) and an evidentiary reference of Sturla et al. (FGFR3IIIS: a novel soluble FGFR3 spliced variant that modulates growth is frequently expressed in tumour cells, British Journal of Cancer (2003) 89, pages 1276 – 1284, published online on 09/30/2003).

Claims 1, 4 and 6-12 are drawn to an *in vitro* method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual, that comprises: a) the detection and/or quantification of the FGFR3 protein in a sample of an individual, wherein the sample is a bladder tissue or urine, and b) the comparison of the amount of FGFR3 protein, of detected in a sample of an individual, with their normal reference values; wherein, increased levels of FGFR3-protein relative to normal reference values

are indicative of bladder TCC, and normal reference values in samples are from subjects without bladder transitional cell carcinoma.

It is noted by the Examiner that the specification does not define the term "FGFR3", and therefore, it has been interpreted according to Applicants' remarks as encompassing "the normal forms of the FGFR3 protein, FGFR3IIIc and FGFR3IIIb" (see Applicant's remarks filed on 01/07/2010, page 12, lines 15-17). As such, the instant rejection was necessitated by Applicants' provision of a definition of the term "FGFR3" in order to overcome the previous 103(a) rejection of record (see above).

Cappellan et al. teach that they "assessed transcript levels of the two FGFR3 variants, FGFR3b and FGFR3c, [which are identical to what Applicants refer to as FGFR3IIIb and GFGR3IIIc, respectively] by semi-quantitative RT-PCR in 76 primary bladder carcinomas, 6 normal urothelia, 29 primary cervical carcinomas and 6 normal cervical epithelia" and FGFR3b was "detected in 70 of 76 (92%) bladder carcinomas and 27 of 29 (93%) cervical carcinomas" (see page 18, right column, lines 6-18). Cappellen et al. further teach that "[t]he expression of a constitutively activated FGFR3 in a large proportion of two common epithelial cancers is the first evidence of an oncogenic role for FGFR3 in carcinomas. FGFR3 currently appears to be the most frequently mutated oncogene in bladder cancer" (see page 19, center column, lines 7-13).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to practice an in vitro method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual comprising: a) the detection

and/or quantification of the FGFR3b protein in a sample of an individual, wherein the sample is a bladder tissue using Western blotting and immunoprecipitation, and b) the comparison of the amount of FGFR3b protein, of detected in a sample of an individual, with their normal reference values; wherein, increased levels of FGFR3b protein relative to normal reference values are indicative of bladder TCC. A skilled artisan would have been motivated to practice such methods because Cappellen et al. teach that *FGFR3b* mRNA levels were "higher" than those encountered in normal bladder (see page 19, center column, lines 2-6), making it an excellent marker for detecting the presence of bladder carcinoma in an individual. Also, it would have been obvious for one of skill in the art to compare the level of the FGFR3b of a subject to that of a normal patient. A skilled artisan would have had a high expectation of success because protein detection techniques such as Western blotting and immunoprecipitation, were rampantly used in the equivalent fields as evidenced by Sturla et al. for the detection of FGFR3 (i.e., see Figure 5 of Sturla et al. on page 1281). While the reference might not teach a specific embodiment of the claims, i.e., a direct comparison of FGFR3 protein levels in bladder cancer tissues versus normal tissues, Cappellen et al. disclose that there is a significant difference in the mRNA level of FGFR3b in bladder carcinomas versus normal bladder epithelia tissues, and it would have been obvious to compare the differential expression of FGFR3 protein in patients with bladder carcinomas from those without the bladder carcinomas. As discussed in KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007), it is considered obvious to combine prior art elements known to be used in equivalent fields of endeavor together into a single combination. The

reference clearly shows that the claimed methods were known to be used in equivalent fields of endeavor; thus, it is considered obvious to combine them together. Therefore, the claimed invention as a whole is *prima facie* obvious over the teachings of the prior art.

Conclusion

Claims 1, 4, 6-12 and 30-38 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on M-F between 9:00-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE/
Examiner, Art Unit 1656

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